

BIOMARKERS: DETECTION AND TREATMENT OF CARDIOTOXICITY

Using biomarkers and early prophylactic treatment to prevent cardiotoxicity in cancer patients on chemotherapy

Giulia Bacchiani* and Daniela Cardinale#

*Cardiology Division, European Institute of Oncology, I.R.C.C.S., Milan, Italy

#Cardioncology Unit, European Institute of Oncology, I.R.C.C.S., Milan, Italy

Address for correspondence:

Daniela Cardinale,
Cardioncology Unit
European Institute of Oncology
Via Ripamonti 435
20141 Milan
Italy

Email: daniela.cardinale@ieo.it

INTRODUCTION

Anticancer therapy can frequently result in serious side effects on specific organs and cardiac toxicity is of considerable concern. Once toxicity develops it may compromise the treatment's clinical effectiveness independent of the oncologic prognosis.⁽¹⁾ The most frequent - and feared - clinical manifestation of cardiotoxicity is the development of left ventricular dysfunction (LVD), that may impact on the patient's survival and quality of life; thus the gain in life expectancy due to anticancer therapy might be compromised by the risk of increased cardiac mortality. Moreover - even when asymptomatic - LVD not only negatively influences patients' cardiologic outcomes - it also seriously limits their therapeutic opportunities when adjunctive oncologic therapy for cancer relapse or persistence is required. The presence of LVD restricts the choice of possible oncologic treatments to the less aggressive and, consequently, less effective options.

Over the last years, the weight of the cardiac toxicity of anticancer treatment has markedly increased due to an improvement in patient survival; an ageing population; the tendency to use progressively higher doses of anthracyclines; the introduction of new anticancer drugs with unexpected cardiac toxicity; and combined treatments with synergistic harmful effects on the heart.^(2,3) According to American cardiologic guidelines, patients receiving anticancer treatment may at present be considered a Stage A heart failure group, namely those with an increased risk of developing LVD.⁽⁴⁾ Avoiding cardiotoxicity has therefore become a primary

ABSTRACT

Cardiac toxicity induced by anticancer therapy is of considerable concern for, once it develops, it may compromise the clinical effectiveness of treatment independent of the oncologic prognosis. The main strategy to minimize cardiotoxicity is to detect high-risk patients and begin prophylactic treatment as early as possible. According to the current standard for monitoring cardiac function cardiotoxicity is usually detected only once a functional impairment has already occurred, thus precluding any chance of prevention. The measurement of cardio-specific biomarkers can be a valid diagnostic tool for the early identification, assessment and monitoring of cardiotoxicity.

The role of Troponin I in identifying patients with subclinical cardiotoxicity and their subsequent treatment with angiotensin-converting enzyme inhibitors to prevent left ventricular ejection fraction (LVEF) reduction and cardiac events, is emerging as an effective strategy against these complications. When this approach is not feasible, a complete LVEF recovery and a reduction in cardiac events may be achieved if left ventricular dysfunction (LVD) is detected early and the patient promptly treated with angiotensin-converting enzyme inhibitors, possibly in combination with beta-blocking agents. SAHeart 2012; 9:250-262

goal for both cardiologists and oncologists. The main strategy to prevent clinical cardiotoxicity is early detection and the initiation of prompt prophylactic therapy.

EARLY DETECTION OF CARDIOTOXICITY

Current approach

Periodic assessment for LVEF is the most widely used non-invasive method for detecting cardiotoxicity LVEF either via echocardiography or multigated acquisition scanning. Although several available guidelines exist none specify how often, by what means or how long cardiac function should be monitored during and after cancer treatment. The recommendations of these guidelines are not consistent and seem to be based on modest evidence.⁽⁵⁾

Though LVEF is a crude index of cardiac function, it is relatively insensitive in detecting anticancer drug-induced cardiotoxicity at an early stage. Usually there are compensatory mechanisms in place to ensure normal overall function in a patient despite an initial reduction in myocardial contractility. As a rule no considerable

change in LVEF occurs before the compensatory mechanisms are exhausted.

Once LVD develops, complete recovery of cardiac function occurs in only 42% of patients, despite optimal pharmacologic therapy.⁽⁶⁾ The diagnosis of cardiotoxicity evidenced by a decrease in LVEF therefore precludes any chance of preventing its development.^(5,7-9) Measuring LVEF also presents a number of challenges with regards to image quality, assumption of left ventricular geometry, load dependency and expertise.⁽¹⁰⁾ Improved accuracy and reproducibility of LVEF measurements is an actual need in patients receiving anticancer therapy, since clinical decision making relies completely on these measurements. Multiple gated acquisition (MUGA) scan can reduce inter-observer variability with the disadvantages of including the exposure to radioactivity and limited information that can be obtained on cardiac structure and diastolic function. Magnetic resonance imaging (MRI) is considered the gold standard for the evaluation of cardiac volumes, mass, and both systolic and diastolic function.⁽⁵⁾ However, high cost and the lack of availability limit the routine use of MRI.

These limitations have prompted investigations into the development of more sophisticated echocardiographic techniques, like contrast echocardiography and real-time 3D-echocardiography, which allow for an improvement in the accuracy of calculating LVEF.^(10,11) Both Doppler tissue imaging and speckle-tracking echocardiography appear to be more sensitive than standard echocardiography in detecting subclinical changes in cardiac performance that anticipate a decrease in conventional LVEF, even if long-term data on large populations, confirming the clinical relevance of such changes, are not available yet.^(10,11)

The role of biomarkers

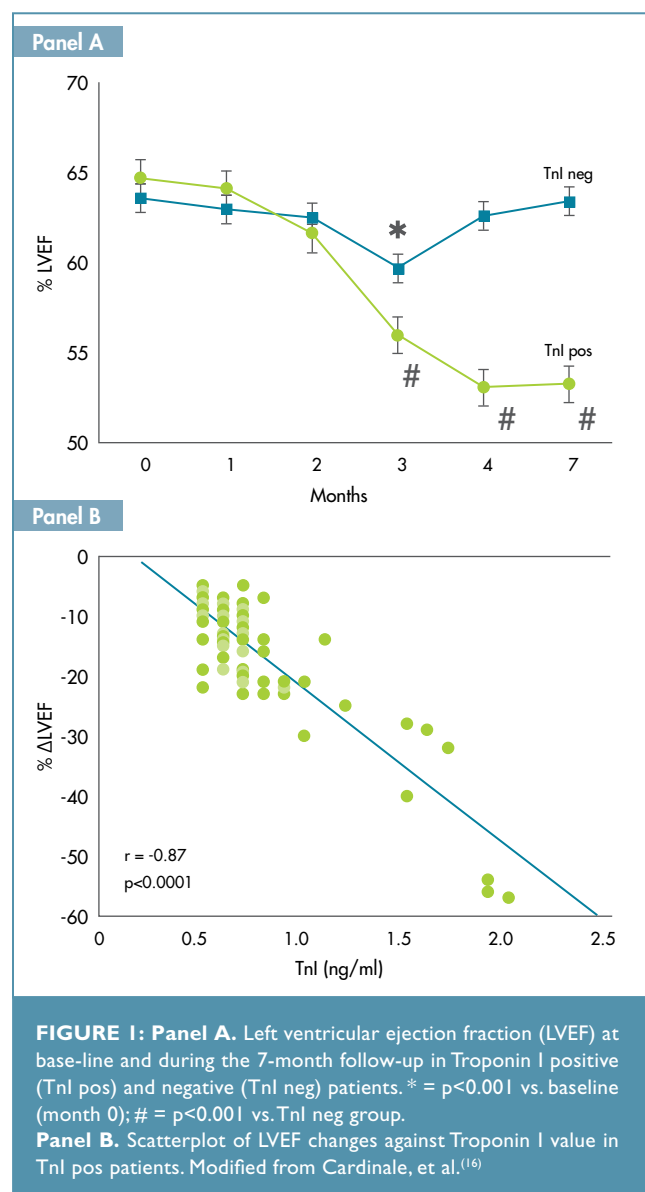
A novel approach based on the use of cardiac biomarkers has emerged in the last decade, resulting in a cost-effective diagnostic tool for early, real time identification, assessment and monitoring of anticancer drug-induced cardiotoxicity. This approach seems to overcome most of the limitations of the techniques described above, as it has proven to be more sensitive and more specific, cheaper, repeatable without damage for the patients, readily available even in small hospitals, and without inter-observer variability.

Troponins

Troponin (Tn) is considered the gold standard biomarker for myocardial injury from any cause.⁽¹²⁾ The employment of cardiac troponins as biomarkers of early chemotherapy-induced cardiotoxicity was initially reported in animal models.⁽¹³⁾ Moving to the

clinical field, Lipshultz, et al.⁽¹⁴⁾ reported that, in children treated with anthracyclines (AC) for lymphoblastic leukaemia, a TnT increase in about 30% of cases, sometimes persisting for months, suggesting that cardiac damage, elicited by AC, may last for a long time. This increase positively correlated with AC dose and predicted morbidity and mortality.

More recently, in the same population, followed-up for 5 years after treatment, the authors observed that children who had experienced at least one raise in TnT during treatment showed late cardiac abnormalities at echocardiography.⁽¹⁵⁾ Further studies have demonstrated that TnI is also a sensitive and specific marker for myocardial injury in adults treated with high-dose chemotherapy (CT), and is able to predict, at a very early phase, both development and severity of future LVD (Figure 1).⁽¹⁶⁻¹⁸⁾ Additionally, in 703



cancer patients, in whom TnI was determined before CT, during the following three days after the end of CT (early evaluation) and after one month (late evaluation), three different troponin release patterns identified patients at different risk of cardiotoxicity. Troponin I was consistently negative in 70% of cases, positive at only early evaluation in 21%, and positive at both early and late evaluations in 9% (Figure 2).⁽¹⁹⁾ During the 3.5 year follow-up, 1%, 37%, and 84% ($p < 0.001$) of patients, respectively, experienced an adverse cardiac event. Thanks to its high negative predictive value (99%), TnI allows us to identify low-risk patients who will not require further cardiac monitoring. In contrast, TnI positive patients require more stringent surveillance, particularly those showing a persistent TnI increase. Indeed, these patients experienced a greater LVD and a higher incidence of cardiac events than patients showing only a transient increase in this marker.⁽¹⁹⁾

Troponin measurements have proven to be useful for the early detection of cardiotoxicity also in patients treated with a standard dose of CT. Auner, et al.⁽²⁰⁾ reported a TnT increase in 15% of patients treated with standard doses of AC. Patients with an elevated TnT level showed a significantly greater absolute decrease in LVEF than those without an elevation in the marker (10% vs. 2%; $p = 0.017$). A significant LVEF reduction was observed in TnI positive patients treated with AC for leukemia.⁽²¹⁾ In addition, an increased TnT level, detected in the first 3-5 days following administration of standard doses of AC, predicted diastolic dysfunction in 34% of patients.⁽²²⁾

Troponins may also be utilised for the early detection of cardiac injury in patients undergoing treatment with new targeted anti-

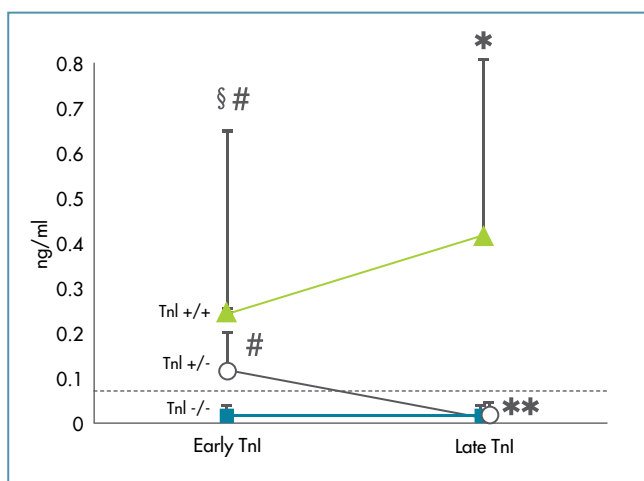


FIGURE 2: Early and Late Troponin I (TnI) values in the 3 study groups. TnI +/+ (n=63;9%); TnI +/- (n=145;21%); TnI -/- (n=495;70%). *= $P < 0.05$ vs. Early TnI; **= $P < 0.001$ vs. Early TnI; §= $P < 0.001$ vs. TnI+/-; #= $P < 0.001$ vs. TnI-/-, Modified from Cardinale, et al.⁽¹⁹⁾

TABLE 1: Major adverse cardiac events in the overall study population and in patients with elevated or normal Troponin I value. (Modified from Cardinale, et al.⁽²³⁾)

	Total (n=251)	Elevated Troponin I (n=36)	Normal Troponin I (n=215)
Severe LVEF reduction ($\leq 30\%$), n (%)	7 (3)	6 (17)	1 (0.5)
Cardiac death, n (%)	0 (0)	0 (0)	0 (0)
Acute coronary syndrome, n (%)	2 (1)	2 (5)	0 (0)
Acute pulmonary oedema, n (%)	1 (0.5)	1 (3)	0 (0)
Heart failure, n (%)	7 (3)	7 (19)	0 (0)
Arrhythmias requiring treatment, n (%)	5 (2)	2 (8)	3 (1.4)
Cumulative events	22 (9%)	18 (50%)	4 (2%)*

LVEF = left ventricular ejection fraction. * $P < 0.001$ vs. elevated Troponin I (by Fisher exact test).

TABLE 2: Elevation of cardiac troponins in patients without overt ischaemic heart disease (Modified from Panteghini M.⁽²⁶⁾).

Acute rheumatic fever
Amyloidosis
Cardiac trauma (including contusion, ablation, pacing, firing, cardioversion, catheterisation, cardiac surgery)
Cardiotoxicity from cancer therapy
Congestive heart failure
Critically ill patients
End-stage renal failure
Glycogen storage disease type II (Pompe's disease)
Heart transplantation
Haemoglobinopathy with transfusion haemosiderosis
Hypertension, including gestational
Hypotension, often with arrhythmias
Hypothyroidism
Myocarditis/Pericarditis
Post-operative non-cardiac surgery
Pulmonary embolism
Sepsis

cancer drugs. The role of Troponin I was assessed in 251 breast cancer patients treated with trastuzumab.⁽²³⁾ TnI was measured immediately before and immediately after each cycle, and resulted as having increased in 34 (14%) of patients. LVD occurred in 62% of patients showing an increase of TnI during trastuzumab treatment, and in only 5% of those with normal TnI value ($p < 0.001$). Patients showing an increase of TnI during trastuzumab treatment had a three-fold lower chance of recovery from cardiac dysfunction and had a higher incidence of cardiac events (Table 1). In this study, therefore, TnI was able to accurately identify patients at risk of developing LVD and, among them, those who will less likely recover

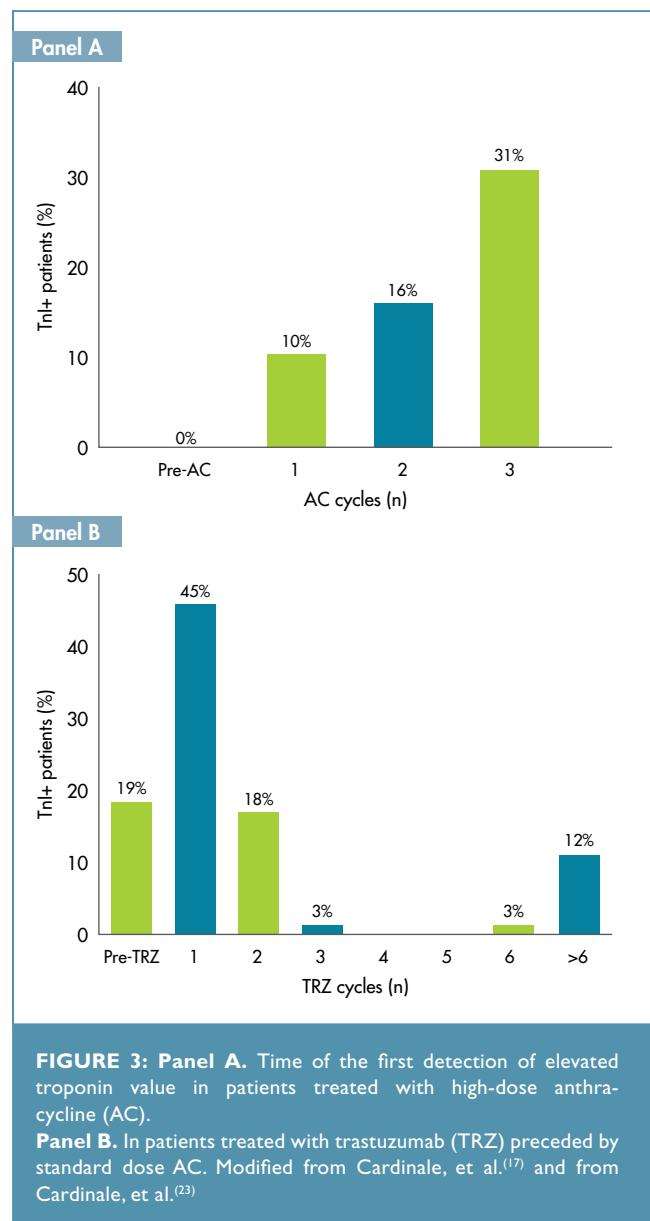
from cardiotoxicity - despite optimised heart failure treatment - thus possibly distinguishing between reversible and irreversible cardiac injury. In a recent study, the timing of maximum detectable TnI value preceded maximum decline in LVEF in patients receiving both trastuzumab and lapatinib - a tyrosine-kinase inhibitor - following AC-based CT.⁽²⁴⁾ In 86 patients with metastatic renal cancer treated with tyrosine-kinase inhibitor sunitinib or sorafenib and monitored prospectively with serial TnT measurements an increase in the markers was observed in 10% of patients. Ninety percent of them showed a decrease in LVEF or regional contraction abnormalities.⁽²⁵⁾ These data suggest that troponins may be useful for assessing cardiotoxicity in patients treated with both old and new antineoplastic treatments. Possibly, the release of troponin reflects a final common event for multiple cardiotoxic mechanisms. As many non-ischæmic pathophysiological conditions can cause myocardial necrosis, and therefore elevations in cardiac troponin concentrations (Table 2), other possible causes of troponin increase must obviously to be excluded.⁽²⁶⁾

Different timing of troponins increase

Following acute ischaemic myocardial damage, troponins show a specific kinetic profile: range of times to initial elevation 3-12 hours, lasting time up to 7 (TnI) or 14 (TnT) days.⁽²⁷⁾ On the contrary, the time course of troponin changes following CT is more variable and less clearly defined. Indeed, data from available studies show that troponins changes might be detected at various time intervals after CT administration, and are possibly due to different troponin release kinetics in response to different treatment schedules containing drugs with possible synergic toxic effect.^(14-16,19-23) Moreover, the sampling protocols used for measurement of troponins were not homogeneous in terms of cut-offs, timing of sampling and cardiac endpoints definition. Standardisation of routine troponin use in this clinical setting is a current need, and future research should focus on the best timing for sampling at which the maximal sensitivity and sensibility from a single sample of troponin can be obtained.

Moreover, additional factors may influence the pattern of troponin release; these include use of variable cumulative doses of anticancer drugs administered, method and timing of administration, and prior drugs exposure.^(28,29) In breast cancer patients treated with high-dose AC-containing schedules, we found that the percentage of TnI positivity progressively increased in parallel with the increasing number of the cycles performed, confirming that the risk of cardiotoxicity in AC-treated patients is dose dependent (Figure 3; panel A).⁽¹⁷⁾ Conversely, in breast cancer patients treated with trastuzumab, we found that the first increase in troponin was most frequent soon after the first cycle of trastuzumab and occurred only in patients previously treated with AC (Figure 3; panel B), suggesting

a possible combined mechanism: TnI rise in these patients possibly reflects AC injury facilitated by trastuzumab, rather than a de-novo cardiac damage.⁽²³⁾ This hypothesis might explain the different timing of the rise in TnI in our studies. Many studies have also elucidated that troponin value can remain elevated for a period ranging from a few hours to several months, after the completion of CT.^(19,20,21,28,30) On the other hand, the exact time-point at which a negative troponin value reaches 100% of specificity for no further troponin release cannot yet be defined,⁽³¹⁾ therefore, repeated blood samples are required to pick out a possible troponin increase. This represents a possible limitation for using these markers in clinical practice. However, this strategy seems to be justified and absolutely cost-effective when negative values allow for the exclusion of most patients from a long-term monitoring programme with an expensive imaging technique.



High-sensitivity troponins

Recently the technological evolution led to the generation of troponin assays with improved sensitivity, enabling a reliable detection of very low amounts of troponin. These assays are referred as “high sensitivity” troponins although definite criteria to define their analytical performance are still lacking. These tests could be of particular interest in the cardiotoxicity field, and may offer some advantages, as often we are dealing with a very low concentration of troponin, and it is of utmost importance to use systems showing high precision also at a very low level.⁽³²⁾

The possible employment of high-sensitivity (HS) troponins in this setting is provided by a recent multicentre study, in which the authors evaluated global and regional myocardial function by tissue Doppler and strain rate imaging, combined with HS TnI, at baseline, and 3 and 6 months during CT including AC and trastuzumab.⁽³³⁾ HS TnI increased in 28% of patients. The decrease in left ventricular longitudinal strain, and a detectable HS TnI, at 3 months were independent predictors of the development of cardiotoxicity at 6 months. On the other hand, changes in LVEF, diastolic function, and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), evaluated at the same time points, were not predictive of later LVD. Further larger investigations comparing HS Tn with traditional troponin assays are needed.

Natriuretic peptides

During the last 10 years several studies have assessed the clinical utility of natriuretic peptides (NP) in the diagnosis and risk assessment of patients with heart failure. Many studies have also investigated their possible role for the diagnosis and prediction of cardiotoxicity induced by anticancer drugs. The first observation, by Suzuki, et al.,⁽³⁴⁾ dates back to the end of the nineties: a persistent elevation of Brain Natriuretic Peptide (BNP) following AC administration was associated with the development of LVD, as compared to patients with only transient elevation. Afterwards, several papers were published, evaluating a total of more than 1 200 patients, with different malignancy (haematologic and solid tumours), age (children and adults) and oncologic treatment (Table 3).⁽³⁵⁻⁵⁵⁾ In most of the studies an association between increased levels of NP and LVD was found. However, only few reports indicated NP as predictors of LVD after anticancer treatment. We conducted a retrospective study including 52 patients receiving high-dose chemotherapy for aggressive malignancies.⁽³⁹⁾ Three distinct increase patterns were found, according to the NT-proBNP trend during the 6 blood samples taken in the 72 hours after CT (Figure 4; panel A). Patients who did not manifest significant echocardiographic changes recorded during follow-up were those who maintained low levels of NT-proBNP for all

the time of sampling (Group A, 32% of patients) or had only a transient increase (Group B, 36% of patients). In patients in whom the level of NT-proBNP increased and remained elevated after 72 hours (Group C, 32% of patients), we observed a deterioration of diastolic indexes (mitral deceleration time, isovolumetric relaxation time, and mitral E/A ratio) and a decrease in LVEF (from 62.8% to 45.6; $p < 0.001$) (Figure 4; panel B), in the following months after the completion of CT. A strong relationship between NT-proBNP value at 72 hours and LVEF changes at 12 months versus baseline ($r = 0.78$; $p < 0.001$) was found. These results are consistent with more recent reports in which a NT-proBNP increase during AC-containing regimens predicted both significant LVD decline and overt HF in adults and paediatric populations.⁽⁵¹⁻⁵⁵⁾ However, the heterogeneousness of data (different populations, sample sizes, kind of NP used, method of measurement, cut-offs, cardiac endpoints, duration of follow-up) makes the comparison of the results from the different studies quite difficult, and it does not allow us to draw definite conclusions or indications regarding the appropriate use of these biomarkers in clinical practice.

Other proposed biomarkers

Other molecules have been proposed as biomarkers for cardiovascular injury related to CT-induced toxic effect.

New markers of myocardial ischaemia and necrosis such as fatty acid binding protein and glycogen phosphorylase isoenzyme BB (brain) have been reported to also increase after CT with AC.^(56,57) However, although these markers are highly sensitive, they have relatively low cardiac specificity and available data are insufficient to propose their use in the follow-up of oncology patients.

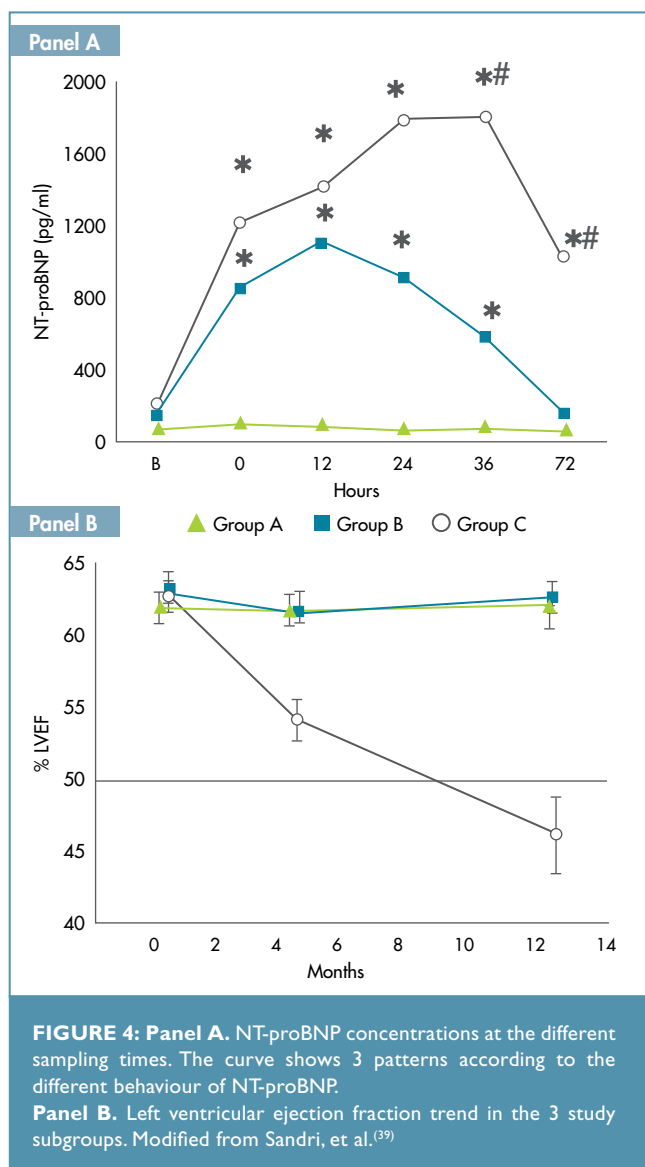
The increase of markers of inflammation, such as cytokines, has also been described after CT. Mercurio, et al.⁽⁵⁸⁾ reported a correlation between interleukine-6 (IL-6) increase and early changes in systolic function when analysed by tissue Doppler imaging in a small population of patients treated with CT containing epirubicin. More recently the same group showed that the angiotensin II receptor blocker telmisartan can reduce AC-induced radical species, antagonise the inflammation, and reverse the early myocardial impairment.⁽⁵⁹⁾ These preliminary results warrant confirmation by further, larger prospective investigations.

Because chemotherapeutic agents can induce endothelial activation, several studies have analysed a possible role of molecules deriving from endothelial damage as markers of cardiovascular toxicity. Nuver, et al.⁽⁶⁰⁾ reported an increased level of endothelial dysfunction markers (tissue-type plasminogen activator and plasminogen activator inhibitor type I) in patients treated with cisplatin-

TABLE 3: Studies on Natriuretic Peptides (NP) as markers of chemotherapy-induced cardiotoxicity.

Author (Year)	Oncologic disease	Adult Child	Pts (N.)	NP evaluated	NP cut-off	Time of sampling Pre-CT CT F-up	Conclusions
Suzuki, et al. ⁽³⁴⁾ (1998)	Haematological malignancies	A	27	BNP	<19pg/ml	X X	Concentrations increased after treatment
Hayakawa, et al. ⁽³⁵⁾ (2001)	Paediatric cancers	C	34	BNP	Not defined	X	Concentrations increased in patients with diastolic dysfunction
Meinardi, et al. ⁽³⁶⁾ (2001)	Breast cancer	A	40	BNP	Not defined	X	Concentrations increased after treatment but was not associated with ventricular dysfunction
Nousiainen, et al. ⁽³⁷⁾ (2002)	Non-Hodgkin's lymphoma	A	28	BNP	Not defined	X	BNP increase associated with diastolic dysfunction
Daugaard, et al. ⁽³⁸⁾ (2005)	Advanced neoplasia	A	107	BNP	Not defined	X X	Not useful to replace estimation of LVEF
Sandri, et al. ⁽³⁹⁾ (2005)	Advanced neoplasia	A	52	NT-proBNP	Dependent on sex and age	X X	Persistent increase is associated with development of cardiac dysfunction
Pinarli, et al. ⁽⁴⁰⁾ (2005)	Non-Hodgkin's lymphoma-Wilms	C	34	BNP	409 ± 226pg/ml	X	Higher NT-proBNP levels are associated with diastolic abnormalities
Nakamae, et al. ⁽⁴¹⁾ (2005)	Non-Hodgkin's lymphoma	A	40	ANP, BNP	Not defined	X	ANP and BNP early increase after CT
Pichon, et al. ⁽⁴²⁾ (2005)	Breast cancer	A	79	BNP	51.3mg/L	X X	BNP predicted development of CHF
Soker, et al. ⁽⁴³⁾ (2005)	Haematological malignancies	C	31	NT-proBNP	Not defined	X	NT-proBNP increased in patients with ventricular dysfunction
Aggarwal, et al. ⁽⁴⁴⁾ (2007)	Haematological malignancies	C	63	BNP	Not defined	X	BNP elevated in patients with late cardiac dysfunction
Zver, et al. ⁽⁴⁵⁾ (2007)	Multiple myeloma	A	23	BNP	25µg/L	X X	BNP levels are sensitive indicator of myocardial injury
Knobloch, et al. ⁽⁴⁶⁾ (2007)	Breast cancer	A	48	NT-proBNP	125pg/ml	X X	NT-proBNP is a marker of acute toxicity
Horacek, et al. ⁽⁴⁷⁾ (2007)	Acute leukaemia	A	26	NT-proBNP	Male 100ng/L, Female 150ng/L	X X	NT-proBNP concentrations correlate with systolic and diastolic dysfunction
Dodos, et al. ⁽⁴⁸⁾ (2008)	Solid or haematological malignancies	A	100	NT-proBNP	Dependent on sex and age	X X	NT-proBNP doesn't predict cardiac dysfunction
Broeyer, et al. ⁽⁴⁹⁾ (2008)	Various malignancies	A	26	NT-proBNP, ANP	Not defined	X X	NT-proBNP is a sensitive marker for the early detection of the course-to-course effects of CT
Mavinkurve-Groothuis, et al. ⁽⁵⁰⁾ (2009)	Various malignancies	C/A	122	NT-proBNP	Male 10pmol/L, Female 18pmol/L	X	NT-proBNP levels are significantly related to LVEDD increase
Cil, et al. ⁽⁵¹⁾ (2009)	Breast cancer	A	33	NT-proBNP	5 - 110pg/ml	X X	Higher NT-proBNP levels are associated with reduced LVEF
Romano, et al. ⁽⁵²⁾ (2011)	Breast cancer	A	71	NT-proBNP	Dependent on sex and age	X X	NT-pro BNP increase was predictive of LV impairment
Roziakova, et al. ⁽⁵³⁾ (2012)	Haematological malignancies	A	37	NT-proBNP	Dependent on sex and age	X X	Persistently elevated NT-pro BNP identifies high risk patients
Sherief, et al. ⁽⁵⁴⁾ (2012)	Acute leukaemia	C	50	NT-proBNP	Dependent on age	X	NT-proBNP correlated with increased LVESD and LVEDD
Lipshultz, et al. ⁽⁵⁵⁾ (2012)	Acute lymphoblastic leukaemia	C	156	NT-proBNP	≥150pg/ml	X X	NT-proBNP correlated with LV thickness-to-dimension ratio

A = adult, ANP = atrial natriuretic peptide, BNP = B-type natriuretic peptide, NT-proBNP = N-type propeptide aminoterminal fragment, C = Child, CK-MB = creatine kinase MB, CHF = congestive heart failure, CT = chemotherapy, ET-I = endothelin-I, F-up = follow-up, LV = left ventricular, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, Trn = troponin I, TrT = troponin T.



based CT for testicular cancer many years before. In a similar population Vaughn, et al.⁽⁶¹⁾ reported that long-term cancer survivors treated with CT showed increased markers of endothelial injury compared to CT-naïve survivors. These findings suggest that CT may induce endothelial dysfunction and accelerate atherosclerotic processes, leading to an increased risk for future cardiovascular diseases.⁽⁶²⁾ However, at present, no correlation with long-term cardiovascular events has been demonstrated, and the predictive role of these markers has yet to be defined.

PREVENTION OF CARDIOTOXICITY

Current possible strategies

To prevent cardiotoxicity, several preventive measures are currently used, including limitation of cumulative AC dose, slowing down of

AC administration, and use of less cardiotoxic AC analogues. However, the addition of cardioprotectants or nutritional supplements and detection of early signs of cardiotoxicity by biomarkers are the two most promising strategies.^(11,63,64)

Addition of cardioprotectants to AC treatment

Carvedilol, a beta-blocker with alpha-1-blocking vasodilatory properties, has also showed strong antioxidant activity that lends it a cardioprotective effect against doxorubicin.⁽⁶³⁾ This favourable effect was confirmed in an in-vitro study⁽⁶⁵⁾ and in a randomised study in which prophylactic use of carvedilol prevented LVD and reduced mortality in a small population of patients treated with AC.⁽⁶⁶⁾

Dexrazoxane, an iron-chelating agent, significantly reduced AC-related cardiotoxicity in adults with different solid tumours and in children with acute lymphoblastic leukaemia and Ewing's sarcoma.^(15,67,68) Moreover, the same agent was more effective than an AC prolonged infusion in preventing cardiotoxicity in 23 Ewing's sarcoma patients treated with doxorubicin.⁽⁶⁹⁾ Nevertheless, dexrazoxane is not routinely used in clinical practice and it is recommended as a cardioprotectant by the American Society of Clinical Oncology only in patients with metastatic breast cancer who have already received more than 300mg/m² of doxorubicin. This might be explained by the suspicion of interference with antitumor efficacy of AC and facilitation of the occurrence of secondary malignancies as well as by its possible myelosuppressor effect. However, meta-analyses didn't find a significant difference in terms of antitumor efficacy and of occurrence of secondary malignancies between patients who were treated with and without dexrazoxane.^(63,67,70,71)

Many other chemical agents have been evaluated such as coenzyme Q10, carnitine, N-acetylcysteine, the antioxidant vitamins E and C, erythropoietin, the endothelin-1 receptor antagonist bosentan, the lipid-lowering agents probucol and statins and some of them showed promising results. Other iron-chelating agents, such as desferoxamine and EDTA, are also of interest (Table 4). Although preliminary findings show that all these agents may have cardioprotective effects their utility in preventing CMP need to be confirmed by further investigation.^(3,11,63,67)

The role of biomarkers in the prevention of cardiotoxicity

A pharmacologic preventive approach extended to all cancer patients treated with CT has a high cost-benefit ratio and exposes patients to possible side effects, including a potential antagonistic effect to antitumor activity of the treatment also in patients less

prone to develop cardiotoxicity. A preventive therapy in selected high-risk patients only, identified by an increase in cardiac biomarkers during and/or after CT, may represent a reasonable alternative. The possibility of identifying patients at high-risk of developing cardiotoxicity by cardiac biomarkers provides a rationale for the development of tailored preventive strategies directed at reducing the clinical impact of cardiotoxicity. Two different strategies could be carried out:

- Use of specific cardiologic treatments given to cancer patients during the oncologic treatment in the attempt to prevent or blunt the rise of these markers or interfere with their persistence after first increase;
- Use of cardiologic treatments given only to selected cancer patients identified by an increase in these markers during CT.

A recent prospective study reported that valsartan, an angiotensin II receptor blocker, given at the same time as doxorubicin was able to prevent an increase in atrial natriuretic peptide, BNP, and left ventricular diastolic diameter and prolongation and dispersion in QTc interval in patients with non-Hodgkin's lymphoma.⁽⁷²⁾ Lipshultz, et al.⁽⁶⁸⁾ reported that TnT elevation occurred significantly more frequently in leukaemic children receiving doxorubicin alone than in those in whose doxorubicin was administered in association with dexrazoxane (50% vs. 21%, respectively; $p < 0.001$).

The usefulness of TnI screening for a selection of patients requiring prophylactic cardioprotective therapy was investigated in a randomised, controlled trial carried out at our institute.⁽³⁰⁾ The cardioprotective effects of enalapril were evaluated in 413 patients treated with high-dose AC. The 114 (24%) patients showing early TnI increase were randomised to enalapril or no treatment. Enalapril was initiated 1 month after the completion of CT, titrated at the maximal tolerated dose, and continued for 1 year. In the enalapril-treated group, LVEF did not change during the follow-up period. Conversely, in patients not receiving enalapril a progressive reduction in LVEF and an increase in end-diastolic and end-systolic volumes were observed (Table 5). Moreover, a significantly lower incidence of adverse cardiac events was found in enalapril-treated patients than in controls at a 1-year follow-up (2% vs. 52%; $p < 0.001$).⁽³⁰⁾

Going from clinical research to the real world we applied this strategy to our daily clinical practice. A treatment with enalapril is usually started in all patients showing a TnI increase after treatment with both old and new anticancer drugs. In more than 1350 treated patients no case of significant reduction in LVEF (below 50%) was observed during a mean follow-up of 4.6 years (unpublished data). These results confirm that this targeted prophylactic approach can be really effective in preventing cardiotoxicity and may be easily and safely applied in daily clinical practice.

TABLE 4: Therapies for reducing anthracycline toxicity.

Agent	Class	Mechanism	Study subject
Carvedilol	b-Adrenergic antagonist	Prevention of free radical formation; prevention of depletion of endogenous antioxidants	Humans
Valsartan	Angiotensin II receptor blocker	Inhibition of Angiotensin II effects	Humans
Dexrazoxane	Chelating agent	Prevention of free radical formation; binding to iron inhibits DNA topoisomerase	Humans
Coenzyme Q10	Dietary supplement	Antioxidant	Humans
Carnitine	Dietary supplement	Antioxidant; transfer of long chain fatty acids into mitochondria	Humans
N-acetylcysteine	Mucolytic agent	Promotion of endogenous antioxidant synthesis	Humans
Vitamin A, C and E	Nutrient	Antioxidant	Animal model/Humans
Erythropoietin	Hormone	Apoptosis prevention	Animal model
Bosentan	Endothelin-1 receptor antagonist	Decrease inflammatory markers (TNF- α) and the expression of apoptotic signaling proteins	Animal model
Probucol	Lipid-lowering agent	Promotion of endogenous antioxidant synthesis	Animal model
Fluvastatin	Statin	Antioxidant	Animal model
Glutathione	Tripeptide thiol	Antioxidant	Animal model
Selenium	Trace element	Antioxidant; anticarcinogenic action	Animal model
Amifostine	Cytoprotective agent	Antioxidant; scavenges reactive oxygen species	Animal model
Desferoxamine	Iron-chelating agent	Production of reactive oxygen species	Animal model

TABLE 5: Echocardiographic parameters during the study period (Modified from Cardinale, et al.⁽³⁰⁾)

		Baseline	Rand.	3 months	6 months	12 months	P value*
EDV (ml)	ACEI-group	101.7 ± 27.4	100.2 ± 26.1	98.1 ± 27.8	97.5 ± 24.5	101.1 ± 26.4	0.045
	Controls	103.2 ± 20.1	103.9 ± 21.0	106.4 ± 21.0	107.1 ± 23.9	104.2 ± 25.6	
ESV (ml)	ACEI-group	38.6 ± 10.8	38.7 ± 10.4	37.3 ± 10.9	37.4 ± 10.3	38.5 ± 11.2	<0.001
	Controls	38.8 ± 10.2	40.5 ± 12.2	49.8 ± 17.6	51.8 ± 16.9	54.4 ± 20.1 [#]	
LVEF (%)	ACEI-group	61.9 ± 2.9	61.1 ± 3.2	61.9 ± 3.3	61.6 ± 3.9	62.4 ± 3.5	<0.001
	Controls	62.8 ± 3.4	61.8 ± 4.3	54.2 ± 8.1	51.9 ± 7.9	48.3 ± 9.3 [#]	

*P value for repeated measures analysis of variance. [#]p<0.001 vs. baseline. EDV = end-diastolic volume. ESV = end-systolic volume. LVEF = left ventricular ejection fraction Rand. = randomisation.

The role of biomarkers in clinical trials

Measurement of cardiac biomarkers, and in particular of troponins, could allow for an early and objective diagnosis of cardiac toxicity in clinical trials evaluating cardiac safety of new antitumoral agents. The usefulness of Tnl monitoring in patients treated with developing molecular targeted therapies has recently been highlighted in phase I trials, by Ederhy, et al.⁽⁷³⁾ Ninety patients with solid metastatic tumours were treated with new anti-VEGF monoclonal inhibitors and tyrosine kinase inhibitors in a phase I trial. All patients were also monitored with serial Tnl measurement. Ten of them (11%) showed an increase in Tnl during the cancer treatment. These underwent echocardiography, cardiac MR, CT scan, and coronary angiography to exclude other possible causes of Tnl rise. Normalisation of Tnl values was obtained with a treatment associating beta-blockers (BB) and aspirin; then all patients were re-challenged with the study drug. No patient experienced any new increase of Tnl, and no cardiac events occurred during the subsequent observation period (mean follow-up: 3 months). The authors concluded that the use of Tnl allows for the early identification of patients more prone to develop cardiotoxicity when exposed to a new drug in cancer clinical trials. These data suggest that patients showing myocardial injury, revealed by the increase in Tnl, should be treated with a prophylactic therapy in order to prevent overt cardiotoxicity and should not be excluded from continuing oncologic treatment. Accordingly, the definition of cardiotoxicity in cancer clinical trials, still based on the evidence of symptomatic heart failure or asymptomatic decrease in LVEF, should be changed moving from a late clinical to an early subclinical definition. As a result the apparent increase in the incidence of subclinical cardiotoxicity due to the low threshold of detection of cardiac injury will be counterbalanced by a lower incidence of clinical cardiotoxicity with a raise in net clinical benefit of the new antitumoral treatment.

TREATMENT OF CARDIOTOXICITY

Anthracyclines-induced cardiotoxicity

Historically, AC-induced cardiomyopathy (CMP) was believed to be refractory to conventional therapy. This opinion was however based either on findings reported in old studies, in which standard therapy included only the use of digoxin and diuretics, or in studies with very small sample sizes.⁽⁶⁴⁾ The response to modern HF therapy of patients with AC-induced CMP has never been fully evaluated because these patients have typically been excluded from large randomised trials investigating novel HF therapies. As a result, the use of angiotensin-converting enzyme inhibitors (ACEI) and BB in this particular clinical setting remain a matter of debate. Moreover the different etiology and age distribution of this kind of CMP when compared with the more frequent ischaemic or idiopathic CMPs raise some concern whether the use of ACEI and BB - recommended for other forms of CMPs - can be directly transferred to this particular clinical setting with similar long-term benefits. Finally as LVD due to anticancer drugs is in most cases asymptomatic many authors have suggested that screening programmes should look for overt HF and current management of LVD induced by anticancer therapy mainly focuses on treatment of symptomatic patients.⁽⁷⁴⁾ This is probably due to the fact that there are special concerns in using ACEI and BB in such a population probably for the fear of unknown pharmacologic interactions. Because cancer patients are considered frail the tendency is not to treat them aggressively. Hence, evidence-based recommendations for the management of cancer patients who develop asymptomatic or symptomatic LVD after CT are still lacking.

In a recent study, the response to modern HF therapy, including ACEI and BB has been prospectively evaluated in 201 patients with AC-induced CMP.⁽⁶⁾ In this study the time elapsed from the end of CT to the start of HF therapy (time-to-treatment) including ACEI

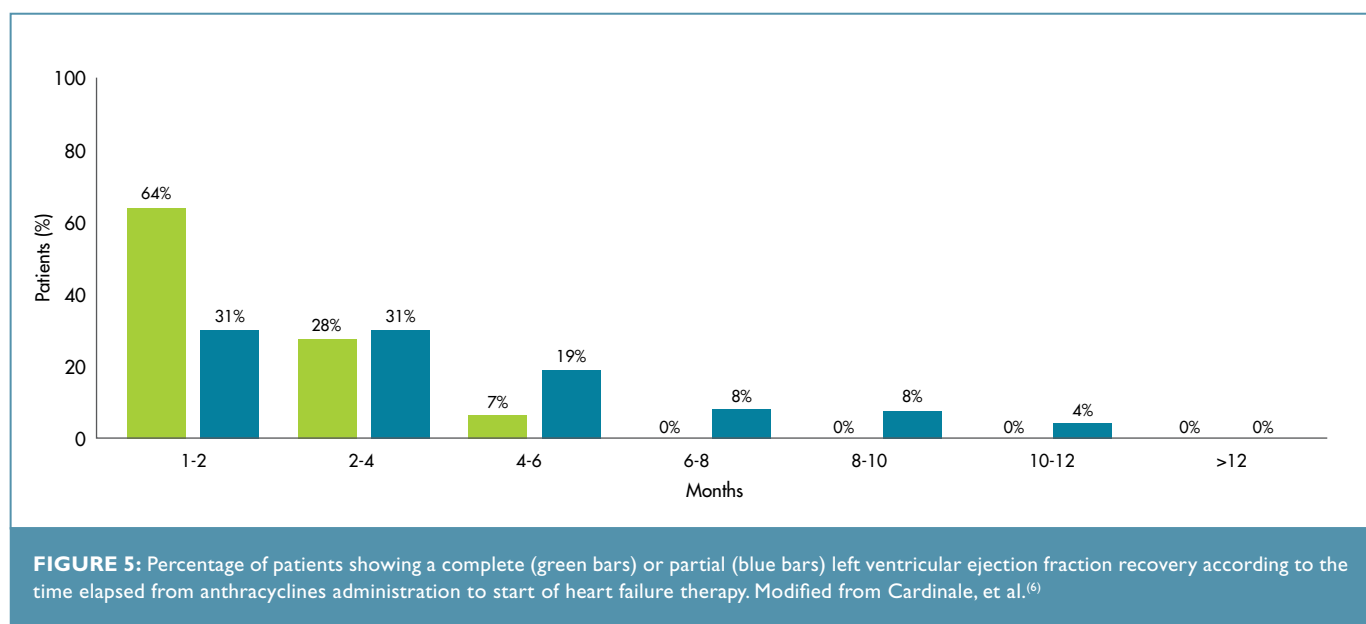
and, when tolerated, BB was a critical variable for recovery from LVD. Indeed, a strong inverse relationship between time-to-treatment and LVEF improvement in response to HF therapy was observed ($R = -0.66$; $p < 0.001$). In particular, the likelihood of obtaining a complete LVEF recovery was higher in patients in whom HF treatment was initiated because of LVD detection within 2 months after the end of CT. After this time limit the percentage of complete LVD recovery progressively decreased and only partial recovery was observed after 6 months. When LVD was detected after 12 months the possibility of obtaining at least a partial recovery was completely exhausted (Figure 5). Notably patients showing complete LVD recovery had a significantly lower rate of adverse cardiac events than those who did not recover (5% vs. 30%). Moreover complete recovery was more frequently observed in patients with asymptomatic LVD than in those with symptoms of HF (56% vs. 11%; $p < 0.001$).⁽⁶⁾ The monitoring of cardiotoxicity based exclusively on symptoms evaluation may therefore hinder the opportunity to detect LVD early in a still asymptomatic and reversible stage. It is also likely that in most previously published studies the poor response to HF therapy was due to under-treatment with ACEI and BB and to late beginning of HF therapy (in most cases it was started more than 12 months after the end of chemotherapy) when LVD has been shown to be no longer reversible. This underlines that an early detection of cardiotoxicity is of pivotal importance and that a prompt therapy based on the association of ACEI and BB should always be considered and undertaken in all cases of anthracycline-induced CMP.

Trastuzumab-induced cardiotoxicity

The incorporation of trastuzumab, a monoclonal antibody targeting human epidermal growth factor receptor 2, to the standard regimens for treatment of breast cancer that over-expresses HER2 receptors - a variant of the disease generally associated with a poor prognosis - has led to a major improvement in outcome.⁽⁷⁵⁾ Its use however has resulted in an unexpectedly high rate of cardiotoxicity which occurs in up to 7% of patients when used as monotherapy and in 28% of patients when associated with AC.⁽¹⁾

Trastuzumab causes a different form of cardiotoxicity from that typical of AC: It is not dose-dependent; AC-typical ultra structural changes are not seen on cardiac biopsy specimens; and it is not caused by oxidative mechanisms.⁽⁷⁵⁾ The clinical outcome of patients who develop trastuzumab-induced cardiotoxicity seems more favourable and cardiac function generally improves after withdrawal on removal of the agent and initiation of HF therapy. Treatment of trastuzumab-related cardiotoxicity is a still controversial issue. Most patients (60-80%) significantly improve their LVD when treated with drugs commonly used for HF such as ACEI and BB.⁽⁷⁶⁾ As patients who developed LVD in the adjuvant trastuzumab trials were not treated in a systematic manner the natural history of trastuzumab cardiotoxicity is currently unknown and evidence-based recommendations for its management are still lacking. Whether trastuzumab-related LVD has a course that is modified with ACEI and BB is still uncertain.⁽⁷⁷⁾

Follow-up data from large trials show that in many patients treated with anthracycline and sequentially with trastuzumab LVD does



not recover; that up to two-thirds of patients continue to receive cardiac medications after complete functional recovery; and that many patients show a LVEF lower than baseline despite optimal HF therapy.⁽⁷⁸⁾ For these reasons some uncertainties on resuming trastuzumab after cardiac function recovery still exist. This is particularly true for patients treated with curative intent while the risk of developing cardiac impairment in the metastatic setting is largely counterbalanced by the benefit of trastuzumab.

CONCLUSION

At present, anticancer treatment-induced cardiotoxicity still remains a serious problem strongly impacting both quality of life and over-

all survival of cancer patients. The most effective approach to minimise cardiotoxicity lays in early detection and prompts prophylactic treatment initiation. The role of TnI in identifying patients at high-risk of cardiotoxicity and their treatment with ACEI is clearly emerging as an effective strategy against this complication (Figure 6). In patients developing LVD after anticancer therapy a complete LVEF recovery and a reduction of cardiac events may be obtained only when LVD is detected early and a treatment with ACEI, possibly in combination with BB, is promptly initiated.⁽⁷⁹⁾

Conflict of interest: none declared.

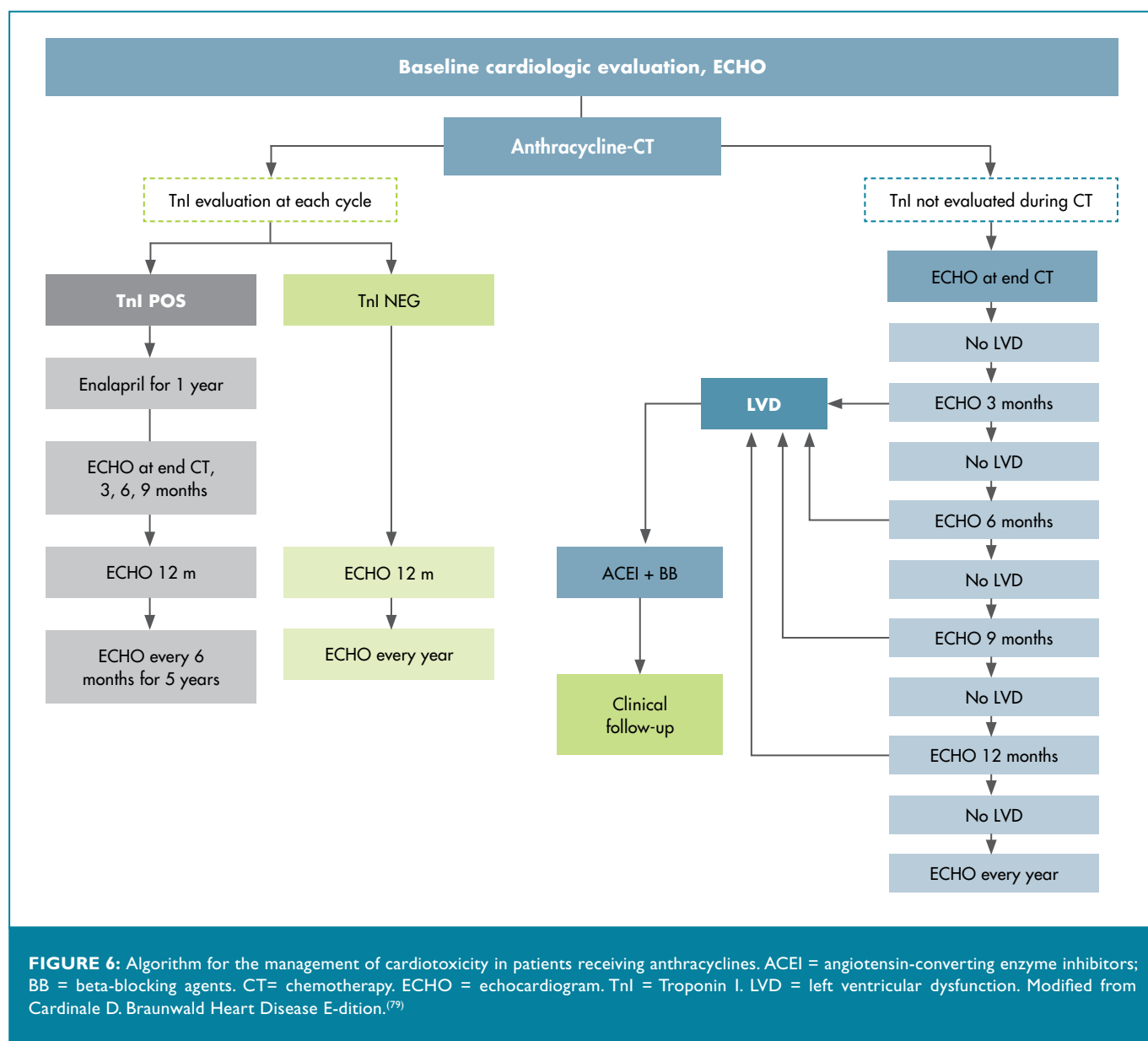


FIGURE 6: Algorithm for the management of cardiotoxicity in patients receiving anthracyclines. ACEI = angiotensin-converting enzyme inhibitors; BB = beta-blocking agents. CT= chemotherapy. ECHO = echocardiogram. TnI = Troponin I. LVD = left ventricular dysfunction. Modified from Cardinale D. Braunwald Heart Disease E-dition.⁽⁷⁹⁾

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